



# Pancreatic neuroendocrine neoplasms — management guidelines (recommended by the Polish Network of Neuroendocrine Tumours)

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**Abstract**

This article presents updated diagnostic and therapeutic guidelines for the management of pancreatic neuroendocrine tumours (PNEN), proposed by the Polish Network of Neuroendocrine Tumours. The guidelines contain new data received in the years 2013–2016, which confirm previous recommendations, and have led to modification of previous guidelines or have resulted in the formulation of new guidelines. Biochemical and imaging (anatomical and functional) tests are of great importance in diagnostics, as well as histopathological diagnosis to determine the management of PNEN patients, but they must be confirmed by an immunohistochemical examination. PNEN therapy requires collaboration among members of a multidisciplinary of specialists experienced in the management of these neoplasms. Surgery is the basic form of treatment in many cases. Further therapy requires a multidirectional procedure; therefore, the rules of biotherapy, peptide receptor radionuclide therapy, molecular targeted therapy, and chemotherapy are discussed.

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**Key words:** pancreatic neuroendocrine neoplasms; functional; non-functional; diagnostics; therapy; guidelines

## Pancreatic neuroendocrine neoplasms (excluding gastrinomas)

### 1.1. Epidemiology, clinical characteristics, and prognosis/survival

The incidence rate of pancreatic neuroendocrine neoplasms (PNEN) or pancreatic neuroendocrine tumours (PNET), both functional (F-PNET/PNEN) and non-functional (NF-PNET/PNEN), is constantly increasing, and is currently approximately 0.32/100,000 people/year. PNENs account for approximately 30% of all gastro-entero-pancreatic neoplasms (GEP NENs). Of all pancreatic neuroendocrine tumours 60–90% are non-functional, usually detected in the advanced stages, due to their slow growth and often asymptomatic or minimally symptomatic character [1–6].

Despite the lack of symptoms of hormonal hypersecretion, they are able to produce certain substances, e.g. pancreatic polypeptide (PP), chromogranin A (CgA), neuron-specific enolase (NSE),  $\beta$ -hCG subunit, calcitonin, neurotensin, and other peptides.

Other PNENs demonstrate hormonal activity (functional tumours), which is reflected in the corresponding clinical symptoms [6–8].

The most commonly described F-PNETs include [7, 9]:

- *insulinoma* — secreting insulin, and
- *gastrinoma* — secreting gastrin.
- The well-documented (> 100 cases) rare functional tumours (RFT) of the pancreas comprise:
  - *glucagonoma* — secreting glucagon,
  - *VIPoma* — secreting vasoactive intestinal peptide,
  - *somatostatinoma* — secreting somatostatin,
  - *GHRHoma* — secreting GHRH — (Growth-Hormone-Releasing Hormone),
  - *ACTHoma* — secreting ACTH — corticotropin,
  - PNET causing carcinoid syndrome — secreting serotonin, tachykinins,
  - *PTHrPoma* — secreting parathyroid hormone-related peptide.

F-PNET may occur in the pancreas and in other locations. The clinical symptoms associated with the presence of such tumours are due to the hormones

secreted by those neoplasms. For very rare tumours, the interpretation of the symptoms is often ambiguous [9, 10].

It should be noted that the existence of somatostatin tumour syndrome as a clinically separate disease entity has been questioned. In a study of 46 patients diagnosed with somatostatinoma, no one, nor any of 821 other PNET patients, presented with a complete set of the proposed signs of the clinical somatostatinoma tumour syndrome [11].

Very rare syndromes associated with F-PNET (1–5 cases) include:

- *reninoma* — secreting renin,
- *LHoma* — secreting luteinising hormone,
- tumour secreting erythropoietin,
- tumour secreting insulin-like growth factor-2 (IGF-2),
- *cholecystokinoma* — secreting cholecystokinin (CCK),
- PNET secreting GLP-1 — glucagon-like peptide-1 (GLP-1).

Most PNETs are sporadic (non-hereditary) tumours, although various rates of F-PNETs occur as components of hereditary syndromes. Multiple endocrine neoplasia type 1 (MEN-1) is the most significant hereditary disease, responsible for 20–30% of gastrin-secreting tumours and < 5% of insulin-secreting tumours or RFT [12–15]. Rare causes of hereditary PNET include von Hippel-Lindau (VHL) disease, von Recklinghausen disease (neurofibromatosis type 1, NF-1), and tuberous sclerosis [12, 13]. Of all VHL patients, 10–17% develop NF-PNET, < 10% of patients with NF-1 almost always develop duodenal somatostatin-secreting tumours, and F-PNET or NF-PNET occur in 1% of patients with tuberous sclerosis [12].

### 1.2. Clinical characteristics of PNEN

#### 1.2.1. Functional pancreatic neuroendocrine neoplasms (F-PNEN)

*Insulinoma* — this insulin-secreting pancreatic tumour is the most common functioning neuroendocrine tumour of the pancreas. In approximately 1% of patients an extra-pancreatic location is possible (duodenum,

Table I. Rare Functional Tumours, RFT [9, 25, 26]

Rare Functional Tumours, RFT	Secreted substance	Frequency	Malignant tumours	MEN-1	Site	Symptoms
Glucagonoma	Glucagon	0.01–0.1/ /1 million/year	50–80%	1–20%	Pancreas 100%	Necrolytic erythema (67–90%), glucose intolerance (38–87%), body weight loss (66–96%), stomatitis, diarrhoea and hypoaminoacidemia
VIPoma [Verner-Morrison syndrome, pancreatic cholera, WDHA syndrome]	Vasoactive intestinal peptide	0.05–0.2/ /1 million/year	40–70%	6%	Body of the pancreas (90%, adults), sympathetic system, liver, adrenal glands	Diarrhoea (90–100%), hypokalemia (80–100%), dehydration (83%), acidosis, rarely skin reddening, hyperglycaemia, glucose intolerance and functional gallbladder disorders; WDHA syndrome – Watery Diarrhoea, Hypokalemia, Achlorhydria
Somatostatinoma	Somatostatin	Very rare	> 70%	45%	Pancreas (55%), duodenum/small intestine (44%)	Cholelithiasis (65–90%), diabetes (63–90%), diarrhoea (35–90%), body weight loss
GHRHoma	Growth-hormone-releasing hormone	Unknown	> 60%	16%	Pancreas (30%), lungs (54%), small intestine (7%), others (13%)	Clinical signs of acromegaly (100%)
ACTHoma	Corticotrophin	Rare	> 95%	Rare	Pancreas (4–16%), others – extrapancreatic location	Cushing's syndrome (100%)
FP-NET causing carcinoid syndrome	Serotonin, tachykinins	Very rare	60–88%	Rare	Pancreas < 1%	Carcinoid syndrome
PTHrPoma	Parathyroid hormone-related peptide	Very rare	84%	Rare	Pancreas	Hypercalcaemic syndrome or, in the case of hepatic metastases, abdominal pain

stomach, bile ducts, or lungs) [6, 16]. Its case incidence rate is estimated at 1–3/1,000,000/year. The highest incidence is observed in the fifth decade of life (between the ages of 40 and 45 years), and slightly more often in females (60%). Less than 10% of all tumours are malignant [9]. Insulinoma is usually single, and only 10% of patients have multiple tumours (often of multiple endocrine neoplasia type 1 [MEN1]). In approximately 4–5% they are associated with MEN1 syndrome [6, 9, 16–18]. Clinical symptoms result from hypoglycaemia rather than from the presence of a tumour (which is usually no more than 2 cm in diameter). Clinical symptoms of neuroglycopenia are: pains and vertigo, blurred vision, double vision, abnormal behaviour, confusion, concentration disorders, retrograde amnesia, drowsiness, hallucinations, delusions, and convulsions. In approximately 12% of patients, loss of consciousness occurs with grand mal seizures [6, 19]. Severe hypoglycaemia may result in death. Decreased blood glucose levels also cause increased secretion of catecholamines, and therefore: paleness, increased perspiration, hand tremors, nausea, palpi-

tations, hunger (often increased body weight), and weakness. Although hypoglycaemic episodes usually occur several hours after a meal, often in the morning, irregularly, and of different durations, in some patients (up to 18%) hypoglycaemia may only occur soon after a meal [20–22]. They may be triggered by physical effort, consumption of ethyl alcohol, or low-calorie diet [6, 9, 10, 17, 23, 24].

Prognosis: in benign tumours — very good; in over 95% of such patients a surgical procedure results in complete recovery. In patients with distant metastases, mean survival time is less than two years. Tumour diameter > 2 cm, Ki-67 > 2%, and various molecular and chromosomal disorders, e.g. loss of 3p or 6q, are factors associated with decreased survival [6, 10, 17, 18, 23, 24].

*Gastrinoma* — these gastrin-secreting tumours are discussed in the section: "Gastroduodenal neuroendocrine neoplasms including gastrinoma — management guidelines (recommended by the Polish Network of Neuroendocrine Tumours)" (see p. 138–153).

Other functional pancreatic NENs, classified as rare and very rare, are presented in Table I and II.

**Table II.** *Very rare syndromes associated with functional pancreatic tumours (F-PNETs) [12–15]*

Very rare syndromes associated with F-PNET	Secreted substance	Malignant tumours	Site	Symptoms
Reninoma	Renin		Pancreas	Arterial hypertension,
LHoma	Luteinising hormone		Pancreas	Lack of ovulation, virilisation in women, reduced libido in men
Tumour secreting erythropoietin	Erythropoietin	100%	Pancreas	Polycythemia
Tumour secreting insulin-like growth factor-2	IGF-2		Pancreas	Hypoglycaemia
Cholecystikininoma	Cholecystikinin (CCK)		Pancreas	Diarrhoea, ulcer disease, weight loss, cholelithiasis
Tumour secreting glucagon-like peptide-1	GLP-1			

Prognosis: in RFT depends on the size of the tumour and the presence of distant metastases. Five-year survival in advanced stages of the disease is estimated at 29–45%. Unfavourable prognosis is determined by: Ki-67 > 2%, presence of distant metastases, chromosomal disorders, and presence of cytokeratin-19 [9, 10, 25–27].

### 1.2.2. Non-functioning pancreatic neuroendocrine neoplasms (NF-PNENs)

Non-functioning pancreatic neuroendocrine neoplasms (NF-PNENs) do not cause the characteristic symptoms of hormonal hypersecretion. In some tumours, immunohistochemical methods have revealed the presence of various hormonal substances produced by these neoplasms, but these are either not secreted into the blood circulation or they are secreted in quantities that do not result in clinical symptoms. Most NF-PNENs are well-differentiated tumours. Their incidence rate is 1.8/1,000,000/year in females and 2.6/1,000,000/year in males. The frequency of their detection increases with age, with peak incidence in the 6th and 7th decades of life. In 3–53% of cases (mean 19%) they are associated with MEN1 syndrome (the frequency is age-related, being higher in elderly patients), and in 13–17% of cases with von Hippel-Lindau (VHL) syndrome [6, 28–32].

Symptoms: NF-PNENs are usually diagnosed late, when they are of a large size, cause pressure on the adjacent organs or invade them, or produce distant metastases [6, 8, 28]. The most common symptoms include: abdominal pain (35–78%), weight loss (20–35%), loss of appetite, and vomiting (45%). Less common are internal haemorrhages (4–20%), jaundice (17–50%), or palpable tumours in the abdominal cavity (7–40%) [6, 8, 33–35]. Some studies demonstrate that hepatic metastases are observed in 32% of patients newly diagnosed with NF-PNET [38]. This value is significantly lower than that observed in previous studies (46–73%) [6, 30, 37–39].

Prognosis: The mean survival time of patients with NF-PNETs in currently available studies is 38 months, with a five-year survival of 43% [8, 30]. The mean survival of patients with distant metastases was approximately 23 months, compared to a 70- and 124-month survival rate in the case of a localised disease [6, 8, 30, 40]. The histological grading of the tumour is also an important factor affecting the survival time [8, 41]. Other unfavourable prognostic factors include: age > 40 years, dynamic development of hepatic metastases (25% increase in their volume over 6–12 months), and occurrence of osseous metastases [6, 8].

Recently, new data has been presented in the literature:

- it has been demonstrated that calcifications in a pre-operative CT examination in patients with PNETs (observed in 16% of cases) correlate with the degree of malignancy and the presence of lymph node metastases in well-differentiated PNETs [42],
- the extent of hepatic metastases, involving one or two lobes, or the presence of other metastases in the abdomen are important predictive factors for survival, regardless of the tumour malignancy (Ki-67) [43],
- it has been observed that in most patients with advanced PNENs the neoplasm progresses. Its best prognostic factor is the Ki-67 index value [44],
- the involvement of lymph nodes and the number of involved lymph nodes in patients with PNENs is of significant prognostic value,
- an absence of symptoms is associated with significantly better prognosis, regardless of the stage of the neoplasm, in particular in NF-PNETs.

Currently, prognosis in patients with PNETs in the course of MEN-1 is uncertain due to the high and constantly improving effectiveness of F-PNET treatment in the course of MEN-1 [12–14].



## 2. Diagnostics

### 2.1. Biochemical diagnostics

The biochemical diagnostics of the hormones and markers secreted by PNENs may be helpful in three aspects: initial diagnosis of the disease, assessment of treatment efficacy, and prognosis.

#### 2.1.1. Functional pancreatic neuroendocrine neoplasms (F-PNENs)

The biochemical diagnostics of all F-PNENs requires evidence of increased serum concentrations of specific hormonal markers (e.g. gastrin in the Zollinger-Ellison syndrome or insulin in insulinoma) in combination with clinical symptoms and laboratory changes indicating hypersecretion of a given, such as excessive secretion of gastric juice in ZES, hypoglycaemia in insulinoma, etc. [6, 11]. In a great number of sporadic PNENs, the type of cells may change and tumours may produce various additional peptides (apart from those specific for the tumour). This is related to the worsening of the prognosis, especially when the tumour ectopically secretes ACTH [6, 45, 46].

Most insulinomas are benign tumours with proper serum CgA levels, which may, however, increase if the tumour is malignant or metastatic. According to some reports, CgA concentration is not always useful in the diagnostics of patients with insulin-secreting tumours (specificity of only 73%), contrary to other PNETs [47].

**A positive Whipple's triad is helpful in diagnosing insulinoma:**

1. Autonomous clinical symptoms suggesting hypoglycaemia.
2. Spontaneous hypoglycaemia.
3. Symptoms resolve quickly following the intake of simple carbohydrates.

There is evidence of reduced glycaemia during the symptoms ( $< 40$  mg/dL;  $2.2$  mmol/L) with uninhibited insulin secretion.

**Previous criteria for diagnosing insulinoma:**

The diagnosis of insulinoma is based on the following criteria:

- documented glycaemia  $\leq 2.2$  mmol/L ( $\leq 40$  mg/dL) and concomitant inadequate concentration of insulin  $\geq 6$  mU/L ( $\geq 36$  pmol/L);
- C-peptide concentration  $\geq 200$  pmol/L;
- proinsulin concentration  $\geq 5$  pmol/L.

Interpretation of the above criteria should include drug-induced hypoglycaemia by verifying the serum and/or urinary levels of sulphonylurea and its metabolites [6, 11].

It should be emphasised that diagnostic criteria of insulin-secreting tumours are constantly changing, and

differ with regard to individual diagnostic propositions or consensus reviews. For instance, the US Endocrine Society proposed the following diagnostic criteria: 1. endogenous hyperinsulinism resulting in symptoms, signs, or both, with glucose plasma concentration of  $< 55$  mg/dL ( $3$  mmol/L), insulin concentration of  $> 3.0$   $\mu$ U/mL ( $18$  pmol/L), C peptide concentration of  $> 0.6$  ng/mL ( $0.2$  nmol/L), and proinsulin concentration of  $> 5.0$  pmol/L. In unclear cases the presence of plasma  $\beta$ -hydroxybutyrate in the concentration of  $< 2.7$  mmol/L and plasma glycaemia increased to  $> 25$  mg/dL ( $1.4$  mmol/L) following intravenous administration of glucagon indicates insulin-dependent (or IGF-dependent) hypoglycaemia. Use of 3 instead of 5  $\mu$ U/mL as the limit value of insulin is supported by a study demonstrating that using a limit value of  $> 5$   $\mu$ U/mL would result in missing 9% of the patients with insulin-secreting tumours [48]. Another study revealed that in certain patients with insulin-secreting tumours (23%) the plasma  $\beta$ -hydroxybutyrate concentration may be  $> 2.7$  mmol/L, especially if the patients underwent partial pancreatectomy, and were examined for any recurrence [48].

Some studies confirm that in patients with MEN-1, insulin-secreting tumours are found more frequently than gastrin-secreting tumours and in 25% of patients insulinoma occurs before the age of 20 years [12, 49, 50]. Therefore, if an insulin-secreting tumour is found in a patient under 20 years old, or if multiple insulin-secreting tumours are found regardless of age, MEN-1 should be suspected, and suitable genetic tests performed [26, 52, 53].

When diagnosing insulinoma, the 72-hour fasting test is still the gold standard, although some studies report that a 48-hour test may be sufficient. The fasting test is performed under inpatient conditions, with serial measurements of the blood glucose concentration. Patients with insulinoma usually develop hypoglycaemia within 24 hours. In 5% of patients, hypoglycaemia may occur after meals [6, 54]. If symptoms of hypoglycaemia occur and the blood glucose level is  $\leq 2.2$  mmol/L ( $\leq 40$  mg/dL), blood should be collected for C-peptide, proinsulin, and insulin assays. The lack of adequate suppression of insulin in hypoglycaemia confirms the presence of an independently secreting insulinoma-type tumour [6, 11].

In one of the studies, the most sensitive criterion for diagnosing insulinoma was the coexistence of elevated proinsulin levels and fasting glycaemia of  $\leq 2.5$  mmol/L ( $\leq 45$  mg/dL) [6, 11].

#### Gastrinoma

The biochemical diagnostics of gastrinoma is discussed in the section on gastroduodenal NENs (see p. 138–153).

### 2.1.2. Rare functional pancreatic neuroendocrine neoplasms (RF-PNEN)

The biochemical diagnostics of RF-PNEN includes confirmation of increased serum concentrations of specific biochemical markers, e.g. glucagon in suspected glucagonoma (positive result > 1000 pg/mL), vasoactive intestinal peptide (positive result > 170 pg/mL), and somatostatin (in the case of pancreatic tumour location, it is over 50 times higher than the reference values) [6].

Chromogranin A (CgA), which is a general marker, may only be used to confirm the presence of a neuroendocrine tumour and monitor the course of the disease, but it cannot constitute the basis for the diagnosis of a functional PNEN syndrome.

All biochemical tests should be performed during the first visit. Suspected Cushing's syndrome due to PNEN should be confirmed in 24-hour urine collection or midnight serum cortisol measurements, or by determination of cortisol concentration in the saliva. If necessary, determination of cortisol inhibition with the use of a suitable dexamethasone suppression test should be performed.

The assessment of markers specific for NENs is useful in the diagnosis and monitoring of various tumours. See Table III [6, 55]. Indications for their determination depend on the clinical status of the patient with PNEN.

Concentrations of certain peptides increase significantly after meals, and may remain increased for as long as six hours following a meal. The blood for testing needs to be collected only in the morning, and under fasting conditions [6, 11]. In the case of CgA this is not required, but if blood samples are not collected under fasting conditions, this should always be recorded to ensure the proper interpretation of the results by the laboratory. One should note that concentrations of all PNEN blood markers, with the exception of insulin, are increased in patients with impaired renal function, so interpretation of the results in this group of patients may be difficult. Among the numerous markers assessed in the blood, CgA is a prognostic factor for most PNENs [6, 56, 57].

### 2.1.3. Non-functional pancreatic neuroendocrine neoplasms (NF-PNEN)

The biochemical in PNEN tests CgA is recommended, which is a marker for most NENs. The level of chromogranin B (CgB) may be elevated if the level of CgA is within the reference range [6, 11, 58].

NF-PNENs can also secrete **pancreatic polypeptide (PP)**. However, the percentage of patients with increased PP concentration is significantly lower than that of patients with increased CgA concentration [11]. The need for standardisation of CgA assays should be emphasised [6, 59, 60].

**Table III. Specific markers for various PNENs (modified according to [6, 55])**

Tumour type	PNEN markers
PNEN	CgA
NF-PNEN	PP, NSE, hCG
Insulinoma	CgA, insulin, glucose C-peptide or proinsulin
Gastrinoma	Gastrin
Glucagonoma	Glucagon, enteroglucagon
VIPoma	VIP
Somatostatinoma	SST
PPoma	PP
MEN1	CgA, gastrin, calcium, PTH, insulin, glucagon, PP

CgA — chromogranin A; hCG — human chorionic gonadotropin; NSE — neuron specific enolase; PP — pancreatic polypeptide; PTH — parathyroid hormone; SST — somatostatin; VIPoma — tumour secreting vasoactive intestinal peptide

In the biochemical diagnostics of *NF-PNENs* the following markers are also used: neuron-specific enolase (NSE), whose sensitivity in NENs of G1 and G2 is 19% and 54%, respectively, and the  $\beta$  subunit of human chorionic gonadotropin ( $\beta$ hCG). Neuron specific enolase is mainly determined in NEC, if the CgA concentration is normal [6].

### 2.1.4. Pancreatic neuroendocrine carcinomas

Concentration of CgA and other hormonal markers in this group of pancreatic NENs usually give negative results. NSE may be used as a marker for these neoplasms [6]. Its sensitivity is approximately 62–63%, and it also forms an independent prognostic factor for NEC [6, 61, 62].

#### *Minimal consensus statement on biochemical tests:*

*Determination of plasma CgA level should be the basic biochemical test in patients with suspected PNENs. In non-functional PNENs, pancreatic polypeptide (PP) can be used (for early detection of PNENs in MEN-1 and PNECs, especially those with low CgA level).*

*Determination of specific markers (gastrin, insulin, serotonin, VIP, glucagon, etc.) should be performed if the patient presents symptoms suggestive of a hormonal clinical syndrome (\*evidence level 3).*

*Specific dynamic tests are performed in individual cases.*

*Diagnostic examinations for MEN-1 are obligatory.*

## 2.2. Pathomorphological diagnostics

### 2.2.1. Pathogenesis and prognosis

The term “pancreatic neuroendocrine neoplasms” refers to tumours arising from a pluripotent stem cell of the

\*evidence level according to OCEMB [252]

pancreatic ducts with neuroendocrine differentiation. The term "islet cell tumour", frequently used in the past, is incorrect due to NEN histogenesis, because these neoplasms do not arise from pancreatic islets [6]. All pancreatic neuroendocrine neoplasms (PNEN) of at least 0.5 cm in diameter are malignant neoplasms, regardless of their histological type. Only a microadenoma of less than 0.5 cm diameter can be a benign form.

### 2.2.2. Diagnostic algorithm

Pathomorphological diagnostics of NENs are based on the standardised World Health Organisation (WHO) classification [63]. The pathomorphological diagnosis is confirmed by immunohistochemical methods, to assess the expression of neuroendocrine markers: chromogranin A (CgA) and synaptophysin, and the Ki-67/MIB1 proliferation index [6]. Immunohistochemical examination of the hormonal substances produced by pancreatic cells is insufficient for the diagnosis of functional or non-functional tumours [64]. Pancreatic cells may demonstrate immunohistochemical expression of the analysed products even in minimal quantities, without any clinical significance.

The histopathological diagnostics of PNENs requires an assessment of:

- histological type according to the WHO 2017 classification [63], comprising well-differentiated NETs, and poorly differentiated neuroendocrine tumours, referred to as neuroendocrine carcinomas (NECs),
- **histological grade (G, grading)**, which is important from the prognostic and predictive points of view, especially in NENs. It is recommended that it is assessed in each case, both in tumours removed surgically and in biopsies, if the quantity of neoplastic tissue is sufficient. The assessment of the G feature is based on two criteria: the number of mitotic figures in 10 high-power fields under a light microscope, with magnification of 40x, and proliferation index Ki-67. The principles for the assessment of these two parameters according to ENETS/WHO are presented in Table IV in "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms" (p. 79–110).

Well-differentiated tumours demonstrate a proliferation index of below 20%, and below 20 mitotic figures in 10 HPF. According to both criteria, the above-mentioned tumours are divided into two groups: NETs of G1 and NETs of G2, as presented in Table IV in *Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms* (p. 79–110). NETs demonstrate intense and extensive immunohistochemical expression of synaptophysin and chromogranin A (CgA). Feature G3 is characteristic of neoplasms with over 20 mitotic figures in 10 HPF, and a proliferation index of over 20%. These

**Table IV. ENETS and TNM AJCC/UICC classification 8. Edition 2017 [65, 69, 70]**

Feature T according to TNM	TNM ENETS	TNM AJCC/UICC, 2017
TX	Tumour has not been assessed	Tumour has not been assessed
T1	Tumour limited to the pancreas, < 2 cm in diameter	Tumour limited to the pancreas, < 2 cm in diameter
T2	Tumour limited to the pancreas, 2–4 cm in diameter	Tumour limited to the pancreas, 2–4 cm in diameter
T3	Tumour limited to the pancreas, > 4 cm in diameter or invading the duodenum / bile tract	Tumour limited to the pancreas, > 4 cm in diameter or invading the duodenum or bile tract
T4	Invasion of adjacent organs or the walls of large vessels	Tumour invading adjacent organs (stomach, spleen, colon, adrenal gland) or walls of the main vessels (coeliac trunk, superior mesenteric artery)

**Table V. Clinical staging of PNENs according to TNM AJCC 8, UICC 8. Edition 2017 [65]**

Clinical stage	Comments
Stage I	T1 N0 M0
Stage II	T2-3 N0 M0
Stage III	T4 N0 M0, any T N1 M0
Stage IV	Any T, any N, M1

tumours may present a low immunohistochemical expression of synaptophysin and CgA. It should be noted that rarely, in certain well-differentiated neuroendocrine tumours (NETs), a high proliferative activity of over 20% and over 20 mitotic figures in 10 HPF may occur. These neoplasms, on the basis of feature G, were previously classified as neuroendocrine carcinomas (NECs). However, due to different prognosis and treatment methods for this group of patients, they have been distinguished from NECs under the term of well-differentiated G3 neuroendocrine tumours (G3 NETs) [63, 65–68]. This classification is presented in Table V in "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms" (p. 79–110).

- **pTNM stage of pathological advancement** according to ENETS [69] and TNM AJCC Eighth Edition of 2017 [65] and UICC 8 2017 [70], which are identical for PNENs. The most reliable assessment of the stage can be made on the basis of an examination of the tumour along with surgically removed lymph nodes, and data regarding the presence of distant metastases.

Feature N, describing the lymph node status, has two degrees: N0 if no lymph node metastases were found, and N1 if metastases to lymph nodes were observed. The number of lymph nodes examined in the surgical material depends on the type of surgery, but 12 lymph nodes are considered optimal. The most recent, Edition 8 of the TNM UICC classification, additionally distinguishes between N1: metastases to 1–3 lymph nodes, and N2: metastases to four or more lymph nodes [70].

Feature M, describing distant metastases, is defined as follows: M0 if no distant metastases were found; M1 if distant metastases were found, with M1a meaning metastases limited to the liver, M1b meaning metastases to at least one extrahepatic organ (lung, ovary, extra-regional lymph nodes, peritoneum, bones), and M1c meaning metastases defined by M1a and M1b.

The clinical staging of PNENs according to TNM UICC 8

- since 2017 [70], it is slightly different.
- Each diagnosis of NEN must be confirmed by immunohistochemical examinations with the use of antibodies against chromogranin A (CgA) and synaptophysin, and by the Ki-67/MIB1 proliferative activity assessment;
- In certain cases, products secreted by NENs, such as gastrin, insulin, or glucagon, may be assessed. These markers are more useful for detecting the metastases of functional tumours, especially if the original site is unknown [65].
- The clinical staging of NENs is presented in Table III.

### 2.2.3. Prognostic indicators in the histopathological report

In the histopathological examination it should be noted that nodules smaller than 5 mm are referred to as microadenoma, and are not considered in the histopathological report. Multiple foci are characteristic for PNENs, especially in MEN1, in over 30% of gastrinoma cases and 13% of insulinoma cases. Therefore, a very careful microscopic assessment of the surgical material, involving cross-sections of the pancreatic parenchyma at 3- to 5-mm intervals, is necessary. In each case, the assessment of resectability is an important prognostic parameter. In order to perform this, it is necessary to evaluate macroscopically and microscopically the surgical margins: of the common bile duct, transpancreatic with the pancreatic duct, retroperitoneal, and radial, created by the posterior wall of the surgical material. Evaluation of the margins of the duodenum, stomach, and other soft tissues forming the surgical margins is recommended, as well as assessment of the vascular and neural invasions, because they are associated with lymph node metastases and shorter life expectancy, according to some clinical studies. Coagulative necrosis,

either local or geographic, is another prognostic factor, because it correlates with a high grade of histological malignancy of the tumour.

The morphological picture of the tumour, comprising tumour tissue architecture and characteristics of its cells, is also reflected in the tumour differentiation stage [6, 71, 72]. Under a light microscope, a pancreatic neuroendocrine neoplasm usually corresponds to a well-differentiated tumour, or a small-cell or large-cell neuroendocrine carcinoma. Organoid structures in the form of solid nests, trabecular or labyrinthine systems, or structures resembling glands and rosettes, are characteristic. They are accompanied by a varying quantity of tumour stroma and numerous blood vessels surrounding the tumour nests. It is worth emphasising that amyloid deposits are typical for a functional tumour such as insulinoma, whereas glandular-like structures and psammomatous bodies are characteristic of somatostatinoma. Features of neuroendocrine tumour cells are well known to differ from other neoplasms. They are small or medium-sized, with acidophilic or amphophilic and granular cytoplasm. The nuclei are round or oval, usually situated centrally in the cell. A typical feature of NEN, which helps to distinguish it from adenocarcinoma, is fine-grained chromatin, referred to as “salt and pepper”. Apart from the above typical features of neuroendocrine tumours, their cells may present a different picture, creating oncocytic, clear cell, fat-rich, and rhabdoid-type variants. Pancreatic neuroendocrine neoplasms may then resemble melanoma, clear cell renal cell carcinoma, or adrenal cortical carcinomas. Diagnostic errors are caused by incorrect differentiation between PNEN and pancreatic ductal adenocarcinoma or acinar-cellular carcinoma, solid pseudopapillary neoplasms, or clear cell carcinoma metastases from other organs.

To sum up, pathomorphological diagnostics of pancreatic NENs requires experience on the part of the pathomorphologist, the co-operation of an interdisciplinary team of specialists, and access to an immunohistochemical laboratory [6].

#### **Minimal consensus statement on pathomorphological examinations:**

*A minimal histopathological report for PNEN should include:*

- *histological type of the neoplasm, considering the division into well-differentiated neuroendocrine neoplasms (NENs), neuroendocrine carcinomas (NECs), and mixed neuroendocrine non-neuroendocrine neoplasms (MINEN),*
- *histological G grading referring to well-differentiated neoplasms (G1 NET, G2 NET, or G3 NET) and NEC, including division between large-cell and small-cell neuroendocrine cancer (the diagnostic criteria are presented in Table IV and V in section 2.2),*



- *pTNM staging according to ENET and TNM AJCC classifications (it is important to provide affiliation of the classification in each case),*
- *assessment of surgical margins.*

*The histopathological diagnosis of NEN must be confirmed by immunohistochemical tests assessing the expression of the neuroendocrine markers: synaptophysin and chromogranin A (CgA), as well as Ki-67 proliferative activity using the MIB1 antigen [6, 73] (\*evidence level 3).*

### 2.3. Location diagnostics

#### 2.3.1. Endoscopic diagnostics

Classical gastrointestinal endoscopy is practically of no relevance for the diagnostics of PNENs [6].

In the case of functional lesions secreting gastrin, the changes in the upper gastrointestinal tracts, including treatment-resistant, severe reflux oesophagitis, often multiple digestive ulcers of the stomach and duodenum, and hyperplasia of the gastric mucosa may justify further diagnostics (*see p. 138–153*).

In rare cases, the lesions, both functional and non-functional, may cause compression of the main pancreatic duct or bile ducts, and once the non-invasive diagnostic methods have been exhausted, endoscopic retrograde pancreatocolangiography plays an important role, especially in therapy [74, 75].

#### 2.3.2. Ultrasonographic examinations

##### 2.3.2.1. Transabdominal ultrasonography

The sensitivity of conventional ultrasonography (USG), mostly performed as the first-line examination in detecting primary tumours and in assessing the staging of the disease, is low for small tumours. On average, ultrasonography detects approximately 30% of primary insulinomas and gastrinomas. The sensitivity of this method increases for detecting hepatic metastases, where it amounts to 50–80%. For larger tumours, mostly non-secreting pancreatic tumours and late-diagnosed glucagonoma, the sensitivity of transabdominal USG is higher [6, 76–78].

Currently, third-generation contrast agents are being introduced to the diagnostic process. They are composed of gas microbubbles in a phospholipid shell, characterised by a long half-life in the bloodstream and enhanced, perfusion-dependent greyscale. Studies are being conducted on the use of contrast enhanced ultrasound (CEUS) for the differential diagnostics of pancreatic tumours, including PNENs [79]. CEUS detects tumours smaller than 2 cm in diameter with sensitivity comparable to EUS (95%). With respect to PNENs, the sensitivity of the method is up to 94%, the specificity reaches 96%, the positive predictive value is 75%, and

the negative predictive value is up to 99%. The image of neuroendocrine neoplasms has a characteristic echo pattern after intravenous administration of the contrast agent: in the arterial phase, echogenicity increases intensively and quickly decreases as the contrast agent washes out in the venous phase [11].

##### 2.3.2.2 Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) enables precise imaging of the pancreas, and it is the most sensitive of the methods currently used in the diagnosis of pancreatic focal lesions (it detects lesions of 1–2 mm in diameter); a negative result of EUS practically exclude the presence of a pancreatic tumour [6, 80]. A biopsy is recommended to confirm the neoplastic character of the lesion [81, 82]. EUS enables:

- locating of hormonally functional neoplasms (diagnosed on the basis of clinical and/or biochemical symptoms);
- obtaining material for histopathological/cytological examination;
- tattooing of small focal lesions before the planned surgical treatment;
- diagnostic imaging of non-functional PNENs;
- screening tests in patients with MEN1.

In the case of small insulin-secreting tumours, EUS sensitivity is up to 94–100% [83–86]. Diagnostic sensitivity of the examination in pancreatic gastrinoma tumours is nearly 100%, but it decreases in the case of multifocal or extra-pancreatic lesions; in the case of gastrin tumours located in the duodenum and outside the pancreatic parenchyma, the sensitivity of the test is estimated to be approximately 50% [6, 84]. Typically, functional tumours in an echoendoscopic image are single, homogeneous, regular, solid lesions with an echo signal reduced comparing to the pancreatic parenchyma (86% of lesions). Normoechoic or hyperechoic nodules are rare. Lesions may be of the form of a cyst in about 10–20% of patients [6].

EUS is also important in differential diagnosis of pancreatic tumours of indetermined character, and in the pre-operative assessment of staging. Specific ultrasonographic features allow distinction between pancreatic carcinomas and neoplasms of neuroendocrinal origin, as well as between functional and non-functional tumours [6, 87]. The usefulness of EUS in the assessment of staging has also been confirmed, particularly for the evaluation of vascular invasion and tumour staging [6, 88, 89].

EUS is also used to perform fine-needle and large-needle biopsies through the gastric/duodenal wall. It is believed that this route of access, compared to percutaneous biopsy, reduces the risk of spreading of the

\*evidence level according to OCEMB [252]

neoplastic cells [6]. The average sensitivity and specificity of EUS combined with biopsy in the diagnostics of pancreatic NENs is 84% and 92.5%, respectively. In a study published this year [90] the authors reported 90% effectiveness of this method in the diagnosis of PNETs, and 43% accuracy in the assessment of the level of differentiation.

At the pre-operative stage it is possible to inject blue dye into the tumour EUS tissue, which enables faster intraoperative localization of the lesion. This method is of particular use in laparoscopic procedures, in which it is impossible to detect the pancreatic lesions by palpation. Moreover, precise localization of the lesion helps to keep a proper resection margin, and preservation of the healthy pancreatic tissue. However, it should be stressed that tattooing may cause acute pancreatitis [6, 91, 92].

MEN-1 syndrome is a particular indication for EUS. The incidence of pancreatic lesions in this group of patients is estimated at 40–80%. Functional tumours can be detected early, due to typical clinical and biochemical symptoms, but non-functional tumours (approx. 50% of lesions) in most patients are diagnosed late, which determines their poor prognosis. EUS is recommended as the most sensitive and cost effective method of monitoring these patients because early detection of a pancreatic lesion enables radical treatment [6].

#### 2.3.2.3. *Intraductal ultrasonography*

Intraductal ultrasonography (IDUS) may surpass EUS in the detection of PNENs. In this method, a probe 2 cm in diameter is introduced into the duct of Wirsung through the duodenoscope channel [6].

#### 2.3.2.4. *Intraoperative ultrasonography*

The sensitivity of intraoperative ultrasound (IOUS) in the detection of small PNENs is similar to that of EUS. The sensitivity of this examination, combined with intraoperative palpation assessment, is up to 97%. In the case of gastrinoma, the sensitivity of the test within the pancreas is close to 100%, but decreases to 58% with an extra-pancreatic location. Intraoperative IOUS also allows detection of multifocal tumours and metastases in the liver,

and the assessment of the distance between the tumour, especially a small one, and the pancreatic duct, in order to properly evaluate the patient's eligibility for tumour resection or enucleation [93]. An IOUS examination is also performed during laparoscopy [6].

### 2.3.3. **Computed tomography (CT) and magnetic resonance imaging (MRI)**

Presently, according to current guidelines, a spiral multidetector CT (multidetector computed tomography, MDCT) and MR imaging are used for the diagno-

sis of parenchymal abdominal organs, including the pancreas. These methods are especially important in assessing the stage of neoplastic disease, and in monitoring the response to treatment [6, 94]. They are also useful for assessing the anatomical location and the resectability of the primary lesion [6].

#### 2.3.3.1. *Computed tomography (CT)*

Computed tomography enables a targeted biopsy from the lesion to be performed. The sensitivity of each imaging method depends on the location and type of tumour [6, 85, 95].

Prior to administration of the contrast agent, functional PNENs are usually isodense, rarely hypodense in comparison to the remaining pancreatic parenchyma, and calcifications are clearly visible. Most tumours are well-vascularised (80% of insulinomas), so MDCT is intensively enhanced in the arterial phase. Metastases demonstrate a similar behaviour. Therefore, the MDCT should cover both the pancreas and liver in the arterial phase. In this phase of the test it is also possible to assess the tumour/coeliac artery relation. In the parenchymal phase only the pancreas is assessed tumour morphology and contrast wash out. The portal venous phase includes the pancreas, liver, and hepatic portal system [6, 96]. Delayed phase scan has been also proposed 150–180 seconds after the administration of the contrast agent, to further assess wash out of the contrast material from the tumour [6, 97]. In typical neuroendocrine tumours, the contrast enhancement should decrease in the delayed phase relative to the arterial phase by at least 60 HU. Other types of enhancement in PNEN include uneven washout of the contrast agent (from over one half of from less than one half of the tumour mass) or slow increase of enhancement if the tumour is more visible in the equilibrium phase, over which the attenuation of the normal pancreatic parenchyma decreases. Such behaviour is characteristic of tumours with a high connective tissue content. In parenchymal and delayed phases, neuroendocrine neoplasms are not always isodense and thus invisible in the CT scan. Some of these neoplasms maintain enhancement or show initial uptake of the contrast agent, in these phases. Slightly enhanced neoplasms are usually poorly differentiated, so the level of enhancement correlates with the patient survival [6, 98–101].

Non-functional tumours present a lower contrast enhancement, and are heterogeneous due to necrotic areas. Calcifications in adenocarcinomas are very rare, whereas in functioning and non-functioning PNENs they are found in at least 25% of cases. In larger tumours the pancreatic duct is dilated, and parenchymal atrophy is observed. Infiltration of the adjacent structures and

distant metastases are the only features that distinguish malignant from benign lesions. Hepatic metastases are detected in the arterial phase of the examination [6, 95].

Due to the shorter scanning time, the reduced number of movement artefacts, and thin (1–2 mm) tissue layers, MDCT enables multi-dimensional and spatial reconstructions that facilitate the imaging of structures smaller than 1 cm, and allow a complete assessment of the vascular invasion of the tumour [100, 101]. The sensitivity of contrast-enhanced MDCT using 1-mm layers in the diagnosis of insulinoma reaches 85–94%, whereas for various types of NENs the sensitivity of multidetector CT is 50–90% and the specificity is 96% [6, 102, 103, 8]. The role of CT scans in the assessment of PNEN includes the description of tumour morphology, with precise localization and in case of any organ-transgressing infiltration, also determination of the adjacent fat tissue invasion, infiltration of the duodenum, common bile duct, stomach, spleen, intestinal loops, adrenal glands, as well as determination of arterial and venous invasion, providing information about the invaded part and the length of the vessel. The description should also contain information concerning enlarged regional lymph nodes and the assessment of the liver for metastases. Assessment according to TNM classification should be possible on the basis of the CT description [6, 7]. The description should also contain the assessment of the tumour's resectability, according to the NCCN criteria [6, 104].

#### 2.3.3.2. *Magnetic resonance (MRI)*

In the diagnosis of PNEN, MRI conducted according to an optimum protocol is of sensitivity similar to that of CT, of 80–90%. MRI offers a higher tissue resolution combined with multi-dimensional imaging. Limitations of this method include: lower availability (in comparison with CT scanning), higher price, longer duration of the examination, and the necessity of patient co-operation. The method is recommended particularly for younger patients to save them ionising radiation exposure, and also in patients whose CT scan is inconclusive. Neuroendocrine tumours are hypointense on T1-weighted images, and hyperintense on T2-weighted images. Intravenous administration of the contrast agent increases the sensitivity of the method [6, 96]. In a multi-phase examination following the intravenous administration of the contrast agent, the images are enhanced similar to the CT enhancement pattern above.

Following contrast administration, a 3D examination in a T1 sequence using a thin layer (1–2 mm) is recommended.

In addition, in MR spectroscopy, which uses chemical shift, it is possible to determine the chemical composition of the tissues. A relatively increased

lipid content in NENs facilitates differentiation in ambiguous cases.

In recent years, a diffusion-weighted imaging (DWI) method has also been used, in which the level of water diffusion limitation in the tissue is assessed. Neuroendocrine tumours, particularly those with a high connective tissue content, cause limitation of the diffusion of water molecules, which generates intense signals in the DWI sequence, accompanied by lowered ADC. DWI is particularly valuable in tumours with a significant connective tissue component, which are poorly or atypically enhanced after intravenous administration of the contrast agent [6, 76, 105].

It seems that well-differentiated PNETs represent higher values in ADC maps than PNECs [6].

#### 2.4. *Radioisotope diagnostics of PNENs*

The recently observed development of diagnostic methods with the use of somatostatin receptor imaging (SRI), also in combination with intraoperative detection with the use of isotope probe, contributes to higher detection rates of PNENs and their metastases. These tests can identify lesions undetected by anatomical imaging methods, increasing the chances of locating the primary focus and determining the actual stage of the neoplasm [6, 107–109]. They may also be the first-line method in the diagnostics of early recurrence, in monitoring the disease, and in choosing a suitable treatment. A positive result of receptor scintigraphy is also the basis for introducing a therapy with a somatostatin analogue (SSA) [6, 108, 110]. SPECT/CT with the use of  $^{99m}\text{Tc}$ -labelled somatostatin analogues is still used in the diagnostics of PNENs, although the optimal radiolabelled somatostatin analogues examination is PET/CT with the use of  $^{68}\text{Ga}$ -radiolabelled somatostatin analogues, to enable a complete assessment of the stage and extent of the disease [111–113]. The sensitivity of somatostatin analogues PET/CT in the case of PNENs ranges from 86 to 100%, and the specificity ranges between 79 and 100% [113–118], excluding insulinoma, for which the estimated sensitivity is lower. PET/CT examination using  $^{68}\text{Ga}$ -somatostatin analogues may affect the management in 13–71% of patients; therefore, it should be a standard procedure in patients with PNENs (considering the slightly lower sensitivity of the test in insulinoma) [118, 119].

Other tracers that can be used in the diagnostics of PNENs include:  $^{18}\text{F}$ -DOPA, especially if the SRI examination results are negative [120, 121],  $^{11}\text{C}$ -5-hydroxytryptophan [121],  $^{18}\text{F}$ FDG (in the diagnostics of fast-growing, aggressive PNENs and NECs with poor prognosis) [122, 123], and labelled glucagon-like peptide analogues [125–127]. Due to the very high expression of receptors for GLP-1 in some neoplasms, estimated at nearly

100% in benign insulin-secreting tumours, scintigraphy with the use of labelled GLP-1 analogues may become a diagnostic method competing with SRI [110, 125, 126].

The next step to improve sensitivity of location diagnostics of small PNETs (gastrinoma, insulinoma) is using an intraoperative radioisotope probe (RGS) [6, 127, 128].

## 2.5. Location diagnostics of different PNENs

### 2.5.1. Insulinoma

Most frequently these are small tumours, less than 2 cm in diameter (60–70% of cases), usually classified as Group 1 according to the WHO classification; they are mostly single (85%) and in 99% of cases are located in the pancreas, with a similar prevalence for all parts of the organ [6, 23]. While conducting location diagnostics in the search for the cause of hypoglycaemia with hyperinsulinism, it should be noted that in approximately 4% of cases the reason is hyperplasia of  $\beta$  cells (nesidioblastosis; NIPHS, non-insulinoma pancreatogenous hypoglycaemia). In the case of insulinoma, the most sensitive imaging examinations include EUS and USG. The usefulness of classical USG, EUS, IOUS, CT, and MRI is discussed in detail in the section concerning the imaging diagnostics of pancreatic tumours.

Another test used in the diagnostics of insulinoma is SRI. It is important to note that only some insulinoma tumours demonstrate somatostatin receptor expression (according to literature, the frequencies of expression for different SSTR types in insulinoma are as follows: SSTR1 — 51%, SSTR2 — 69%, SSTR3 — 62%, SSTR4 — 39%, SSTR5 — 66%) [6, 107]. If the results of other imaging tests are negative, a PET/CT scan may be performed with  $^{68}\text{Ga}$ -somatostatin analogue  $^{68}\text{Ga}$ -DOTATOC, and  $^{68}\text{Ga}$ -DOTATATE (the sensitivity of a test with labelled  $^{68}\text{Ga}$  DOTANOC and DOTA-Nal3-Octre is relatively low [25–31%]) [112, 129]. Where PET techniques are not available, an examination with Tc99m-labelled SSA can be performed (SPECT/CT).

In insulinoma it is also possible to use angiography with selective arterial calcium injection; however, this test is performed very rarely [130–132]. The method can be used if other imaging techniques do not enable locating of the focal lesion [23]. In the near future, GLP-1 analogue will probably play an important role in the diagnostics of small, difficult-to-detect insulinomas [6, 124–126].

### 2.5.2. Gastrinoma

The tumour is discussed in detail in the section on gastro-duodenal NENs.

A gastrinoma is typically to be found within the triangle of the pancreatic head — duodenum — hepatic hilum. In 48–60% of cases, lymph nodes and hepatic metastases are present at the diagnosis, but in

some groups of patients the proportion of malignant tumours is up to 90% [6, 135]. Multifocal lesions are also possible. The usefulness of USG, EUS, intraoperative USG, IOUS, CT, and MRI examinations are presented in the section concerning the imaging diagnostics of pancreatic tumours.

Other examinations used for the diagnostics of gastrinoma include SRI. The sensitivity of gastrinoma detection according to different authors ranges between 50 and 100% (the literature data reveal the following frequencies of expression for individual receptor types: SSTR1 — 71%, SSTR2 — 50%, SSTR3 — 92%, SSTR4 — 78%, and SSTR5 — 81%) [6, 134]. SRI is the best examination to assess the early stages of the disease and the presence of distant metastases, but the sensitivity of the test decreases to 50% if the tumour is smaller than 1 cm [6, 112, 135]. The preoperative staging should involve at least SRS, and preferably a PET/CT examination with the use of  $^{68}\text{Ga}$ -somatostatin analogues [8, 136]. If PET/CT is available, it should be the first-line imaging diagnostic test [113], and, where it cannot be conducted, SRS/SPECT in combination with EUS and oesophagogastroduodenoscopy should be performed. In the case of rapidly progressing NETs of G1/G2, a PET/CT examination with  $^{18}\text{F}$ FDG should be considered [122].

In the future, the diagnostics of gastrinoma could include scintigraphy with GLP-1 analogue, due to GLP-1 receptor expression on the surface of this tumour.

In the location diagnostics of small tumours, the combined use of several diagnostic methods seems reasonable, and in certain cases also performance of an angiography (the sensitivity of angiography is estimated at 30–50%). In the case of a gastrinoma located in the duodenum, intraoperative transluminescence is also used [6].

### 2.5.3. Location diagnostics for glucagonoma, VIPoma, somatostatinoma, non-functional tumours, and ACTHoma

At the moment of diagnosis, glucagonoma, somatostatinoma, and non-functional tumours are usually large (approximately 5–6 cm), whereas VIPoma is slightly smaller (approx. 2 cm). The lesions are usually diagnosed late, and in approximately 70–90% of cases metastases are found already at the diagnosis [6, 26, 134]. Due to the size of the lesions, they are easier to find by means of classical imaging methods (USG, CT, MRI). SRI, whose diagnostic sensitivity is 70–100%, is a standard examination in the assessment of primary lesions and clinical staging (detection of metastases to the liver, lymph nodes, adrenal glands, spine), and in qualification for receptor radiotherapy [6, 26, 135]. SSTR1 and SSTR2 expression is observed mostly in glucagonoma, SSTR5 in somatostatinoma, SSTR2 in VIPoma, and SSTR1, SSTR2,



SSTR3, and SSTR5 in non-functional neoplasms. Rare ACTHoma neoplasms also demonstrate somatostatin receptor expression. In the case of rare functional pancreatic tumours, EUS is not recommended as the first-line procedure, but it may be used when the MDCT, MRI, and SRI results are inconclusive. EUS may be useful in pre-operative diagnostics, whereas it is rarely necessary in patients with hepatic metastases [6, 9].

#### 2.5.4. Pancreatic endocrine carcinomas

In the location diagnostics of poorly differentiated, fast-growing PNENs, as well as NECs and their metastases, all imaging examinations may be used: USG, CT, MRI, <sup>18</sup>FDG PET/CT, and SRI in tumours with overexpression of somatostatin receptors [6].

##### *Minimal consensus statement on imaging and radioisotope examinations:*

*In the diagnostics of pancreatic neuroendocrine neoplasms, both classical imaging techniques and nuclear medicine tools are used.*

*In non-functional PNENs:*

- multiphase CT and MRI are the basic tests,
- another SRI examination.

*In functional PNENs:*

- SRI,
- Next examination is EUS and multiphase CT/MRI.

*The EUS examination should be performed in each case of a clinically diagnosed functional tumour, and if there are indications for a biopsy.*

*In pancreatic NECs and in the case of fast-growing PNETs, in individual clinical cases, <sup>18</sup>FDG PET/CT can be used (\*evidence level 3).*

### 3. Treatment

#### 3.1. Surgical treatment

##### 3.1.1. Surgical treatment of well-differentiated pancreatic NETs of G1/G2

##### *General principles*

Surgical treatment is the therapy of choice in the case of PNENs because it is associated with significantly prolonged patient survival [8]. The development of diagnostic methods has improved the detection of small, asymptomatic, incidental NF-PNETs [136, 137] (\*evidence level 3). Most non-functional neoplasms ≤ 2 cm in diameter are benign and demonstrate a moderate risk of becoming malignant. In certain cases, tumours ≤ 2 cm in diameter, diagnosed accidentally, may be observed. This applies to asymptomatic G1 or G2 tumours with low Ki-67%, especially those located in the head of the pancreas, if malignancy is not suspected on the basis of a radiological examination, and after consideration of

individual patient characteristics (age, patient's decision, comorbidities) [11]. Due to the lack of clear recommendations, the decision on the course of treatment should be taken by a multidisciplinary team of doctors experienced in the management of PNETs (\*evidence level 4). When choosing a surgical treatment, it is necessary to consider the early and long-term effects of this therapy. According to the WHO classification, there is a correlation between tumour size and its potential malignancy. Tumours > 2 cm, depending on their characteristics, require a pancreatic parenchyma-saving or an extensive resection (\*evidence level 3) [11]. Symptomatic tumours, regardless of their size, usually require a resection.

In MEN-1, if multiple lesions occur, it is recommended to remove them preventively before they become malignant; however, this approach in the case of small, non-functional tumours is still controversial (\*evidence level 3) [6, 8]. The presence of numerous nodules sometimes requires a whole-organ resection. It is known that non-functional tumours associated with MEN-1 should be removed if they are over 2 cm in diameter, metastatic, and fast-growing (increase of > 0.5 cm per year) [11] (\*evidence level 3).

The type of surgical treatment for PNET depends on its size, location, invasion of the adjacent organs, presence of distant metastases, the patient's general condition, and the ability to control the clinical symptoms (\*evidence level 4). Patients are qualified for a radical or palliative treatment, which only improves the quality of life (\*evidence level 4). In the case of tumours located in the head of the pancreas, pancreatoduodenectomy is performed; whereas in tumours located in the body or tail of the pancreas, circumferential resection is conducted, with or without splenectomy (\*evidence level 4). In certain cases of small and well-demarcated PNETs, atypical resections may be performed, including enucleation and resection of the middle segment, also using a laparoscopic technique (\*evidence level 3) [138, 139]. Resection of the middle segment is performed primarily in the case of small lesions located in the pancreatic body. In certain cases, central pancreatectomy is performed with a Roux-en-Y anastomosis of the pancreatic tail with a loop of the small intestine, and closing off the body of the pancreas. The condition of tumour enucleation is continuity of the duct of Wirsung [8]. Resection is necessary if the tumour is located < 3 mm from the pancreatic duct [9]. Enucleation of the lesion entails the risk of damaging or closing the duct of Wirsung, which is associated with complications [140]. These include acute postoperative pancreatitis and pancreatic fistula. Apart from the above complications, resection of a large part of the pancreas may cause the symptoms

\*evidence level according to OCEMB [252]

of exocrine and endocrine pancreatic insufficiency [141]. Tumour resection should be considered even in the presence of metastases, including hepatic metastases, if they are potentially resectable, and the patient meets the criteria for the surgery (*\*evidence level 4*) [7, 142]. As pancreatic tumours are often malignant, it is necessary to remove the regional lymph nodes during resection (*\*evidence level 3*) [7, 141, 143]. In the case of enucleation and resection of the middle segment, it is also recommended to remove lymph nodes for histopathological examination [8, 140]. It is generally believed that G3 PNETs should not be operated on if disseminated metastases were found in the diagnostic process (*\*evidence level 3*) [7]. Resection should be performed only in those centres specialising in surgery of the pancreas. In the case of PNET, an intraoperative USG examination is recommended.

Currently, laparoscopic resection of the pancreas is increasingly common, but the decision concerning the use of the “open” or laparoscopic method should be taken by a pancreatic surgery specialist in the referential centre (*\*evidence level 3*). Circumferential resections and laparoscopic enucleation of pancreatic tumours are currently considered to be safe.

The most common functional tumours are insulinoma and gastrinoma, whereas other tumours are rare (RF-PNET, rare functional pancreatic neuroendocrine neoplasms) [9].

#### **Gastrinoma, Zollinger-Ellison syndrome (ZES)**

A gastrinoma is most often located in the head of the pancreas; in 60–90% of cases it is a malignant neoplasm, and due to the frequent invasion of the lymph nodes there are indications for regional lymphadenectomy [6, 144]. It is recommended that the lesion be removed radically to prevent hepatic metastases, which considerably worsen the prognosis. The scope of the procedures depends on the tumour location and size, and comprises enucleation, resections of the middle segment, distal resections, and pancreatoduodenectomies [6, 143].

The role of surgical treatment in patients diagnosed with ZES without MEN-1, and with negative results of the pre-operative imaging tests (no visualisation) is disputable [6, 11]. A recent study revealed that all patients with sporadic ZES benefit from surgical exploration with the intent to treat. This applies both to patients with tumours visualised during imaging tests before the surgery, and to those whose tumours were not shown in pre-operative imaging examinations [145] (*\*evidence level 3*). This study demonstrated a higher rate of tumour-free individuals after resection, and a higher 20-year survival rate among the patients with negative results of the imaging examinations

than in those with positive results. Tumours were detected in > 98% of patients, regardless of tumour visualisation or lack thereof in imaging examinations. Therefore, in the case of all patients with ZES without MEN-1, who do not present medical contraindications for the procedure, it is recommended that surgical exploration be performed by a surgeon experienced in the treatment of neuroendocrine tumours [11] (*\*evidence level 3*). As gastrinomas are often multiple tumours and occur in the duodenum, careful examination of the abdominal cavity and pancreatoduodenal field during the surgery is recommended, possibly including a duodenotomy [11].

Apart from the prognostic value of lymph node metastases, studies on gastrinoma revealed that lymphadenectomy may extend survival [146, 147] (*\*evidence level 3*). This supports the idea of removing lymph nodes in the tumour area during every surgery involving gastrin-secreting tumours. Surgical resections of tumours with angioinvasion are controversial. Recent reports on resectability in 91% of cases with 10-year survival rates of 62% support the claim that surgical resection should be considered also in patients with PNETs, who demonstrate, under pre-operative examinations, tumour pressure on vessels or angioinvasion, and the decision should be taken by a team of specialists [11, 148, 149] (*\*evidence level 3*).

In Zollinger-Ellison syndrome, which is a part of MEN-1 syndrome, in the case of NF-PNETs or a tumour ≤ 2 cm in diameter, surgical treatment is not typically recommended. Surgical therapy is indicated if the tumour size is over 2 cm. This approach is intended to prevent metastases [142] (*\*evidence level 3*). According to some authors, pancreatoduodenectomy is the recommended procedure (for tumours located in the head of the pancreas) because less extensive procedures are associated with recurrence in 90% of cases [9, 144]. However, current routine management does not include PD, and enucleation remains the recommended surgical procedure [11].

In MEN-1/ZES patients with numerous, small gastrin-secreting tumours and metastases to the lymph nodes, only an extensive surgery, such as pancreatoduodenectomy or complete resection of the pancreas, forms a curative procedure. However, these procedures are not recommended currently as standard management, due to possible early and long-distance complications, the fact that patients with PNETs ≤ 2 cm in diameter demonstrate good long-term prognosis (even 100% survival rate after 15 years of observation), and the possibility to control excessive secretion of gastric juice in MEN-1/ZES patients with pharmacology [9, 11, 150].

\*evidence level according to OCEMB [252]

**Minimal consensus on surgical treatment of gastrin-secreting tumours**

- All patients with sporadic gastrin-secreting tumours, who do not present
- contraindications for surgical procedure, should undergo
- surgical exploration performed by a surgeon experienced in the treatment of
- neuroendocrine tumours [145].
- During every surgery of gastrinoma, lymph nodes in the tumour area should be removed, as this demonstrates a prognostic value and can increase the rate of cured cases.
- Surgical resection should be considered by a team of experienced surgeons in
- PNET patients who demonstrate tumour pressure on vessels or angioinvasion in the pre-operative examinations.
- In patients with MEN-1/ZES with PNET  $\leq 2$  cm in diameter, or in whom NF-PNET

is visible in the imaging tests, routine surgical exploration is not commonly recommended. In patients with PNETs  $> 2$  cm in diameter, enucleation remains the recommended surgical procedure, and pancreatoduodenectomy is reserved for individual, selected cases [9, 150].

**Insulinoma**

Insulinomas are benign in 90% of cases; their removal does not require regional lymphadenectomy and, where the precise preoperative location of the tumour is known, laparoscopy is effective [6, 151] (\*evidence level 1).

In most cases, enucleation of an insulin-secreting tumour is possible, whereas in others more extensive resection is required [152] (\*evidence level 1). In the case of a suspected malignant insulinoma or recurrence of the tumour, radical treatment is recommended, including excision of the recurrence and any possible hepatic metastases [9]. Endoscopic or percutaneous ablation therapies have also been described. In the case of insulinoma, both in patients with sporadic tumours and with MEN-1, EUS-controlled ablation with ethanol, or RFA controlled by CT control or other visualisation methods, was effective [152] (\*evidence level 1). It has been documented that, following EUS-controlled alcohol ablation, patients remain free from disease symptoms for many years [6, 153].

**Minimal consensus on surgical treatment of insulin-secreting tumours**

- A surgical procedure is recommended in all patients with insulin-secreting tumours with
- or without the presence of MEN-1 syndrome, with the exception of non-resectable metastatic tumours.
- Laparoscopic procedures are recommended in patients with sporadic tumours and tumours found in imaging examinations [154].

- In patients who are not eligible for surgical treatment, cases of ablation therapy using endoscopic or percutaneous methods were described for insulinoma [152].

**Rare (RF-PNETs) and very rare functional tumours**

In this group of tumours, radical treatment is recommended, and the scope of resection and lymphadenectomy corresponds to that performed due to gastrinoma.

**Minimal consensus on surgical treatment of RF-PNETs**

- Resection with the intent to treat remains the recommended option in all patients
- with rare or very rare functional PNETs, with the exception of patients with non-resectable metastatic lesions [9].
- Laparoscopic methods can be used in RF-PNETs visible in imaging examinations [9, 139].
- In patients with MEN-1 with PNET  $\leq 2$  cm in diameter or NF-PNET found in imaging tests, routine surgical exploration is still not generally recommended. In patients with PNETs  $> 2$  cm in diameter, enucleation/Local intra-operative resection remains the generally recommended surgical procedure to perform, while pancreatoduodenectomy is reserved for special, individual cases.

**Surgical treatment versus observation of NF-PNETs**

Some studies have assessed the safety and possibility of the non-operative treatment of asymptomatic, sporadic NF-PNETs  $\leq 2$  cm in diameter, particularly in cases which would otherwise require extensive resections [11, 155–157] (\*evidence level 3). According to most authors, a conservative approach seems to be a safe option because most of the observed tumours did not reveal any significant changes in the follow-up period [155, 158] (\*evidence level 3). However, some studies demonstrated that tumours  $< 2$  cm may invade the lymph nodes and can be associated with distant metastases [157, 159–163] (\*evidence level 3). According to some authors, a change in the size of tumours, which can be safely left for observation, should be considered, from  $\leq 2$  cm to  $\leq 1.5$ – $1.7$  cm [160, 162] (\*evidence level 3).

**Advanced F-PNETs**

In advanced functional PNETs, resection is intended to reduce the symptoms and the tumour mass. Cytoreduction may be considered if removal of over 90% of the tumour mass is possible, even if hepatic metastases are present [164] (\*evidence level 3). Removal of 90% of the visible tumour mass is possible in only 5–15% of cases [165]. Cytoreduction may be performed with radiofrequency thermoablation (RFA) (\*evidence level 3), which can also be conducted laparoscopically or percutaneously under CT control. This method may be used if the number of focal lesions in the liver is lower than 10, and the largest

\*evidence level according to OCCEMB [252]

one is < 5 cm in diameter (optimally 3 cm). This method enables the control of symptoms in over 90% of patients [166]. Radical excision of hepatic metastases is the “golden standard” in the therapy of advanced PNETs; therefore, resection should be performed whenever possible (*\*evidence level 4*). The method of resection depends on the patient’s general condition, the size, location, and number of metastases, and whether it comprises enucleation, wedge excision of a fragment of the liver, excision of a segment(s), non-anatomical resection, or hemihepatectomy. R0 resection should be the target in the case of removal of hepatic metastases. Cytoreductive procedures are acceptable [167, 168] (*\*evidence level 2*). Resective treatment of hepatic metastases of PNETs is considered only in NETs of G1 and G2 [164] (*\*evidence level 3*). It depends on the resectability of the lymph nodes, lack of micronodular or non-resectable dissemination in the peritoneum, or distant metastases outside the abdominal cavity [169]. Recent studies emphasise the significance of simultaneous surgical resection of advanced primary PNETs with hepatic metastases, and the associated low number of deaths and post-operative complications [148, 170] (*\*evidence level 3*). However, simultaneous pancreateoduodenectomy and extensive hepatectomy should be avoided due to the high number of complications [170]. Excision of the primary tumour, lymph nodes, and hepatic metastases, combined with thermoablation, may reduce the tumour mass by more than 90% [169]. In the case of unresectable metastatic lesions in the liver, cholecystectomy should be performed during surgery to prevent ischaemic complications of the gallbladder resulting from possible implementation of (chemo) embolisation. Resection of hepatic lesions may be performed in one or two stages, depending on the location and size of the metastases [140]. Other methods for the treatment of metastases include so-called locoregional therapies (variants of ablation, embolisation) and liver transplantation. It is assumed that transplantation is conducted in selected groups of patients with exacerbated symptoms associated with hormonal secretion. Patients who may benefit from transplantation are those under the age of 50 years, without metastases outside the liver, and with a low expression of Ki-67 [143].

If resection of hepatic metastases is impossible, the recommended palliative treatment methods include selective hepatic artery embolisation (HAE), transarterial chemoembolisation (TACE), or embolisation with the use of a radioisotope (*\*evidence level 3*). Currently, these methods are considered to be safe [82, 149]. RFA, cryoablation, and microwave ablation (MWA) can be used for tumours ≤ 5 cm [165].

Resection of a resectable stage IV primary tumour is under consideration [171] (*\*evidence level 3*). In certain cases of unresectable hepatic metastases, macroscopic intraperitoneal lesions may also be removed during the primary tumour resection, so that further treatment stages do not concentrate primarily on the liver [172]. There is no consensus on the simultaneous resection of hepatic and intraperitoneal lesions [173]. If extensive surgery of the liver with the resection of peritoneal lesions is necessary, dividing the procedure into stages, conducting the resection in a specialist centre, and introducing multidirectional treatment should be considered [174]. Currently, the combination of surgery and perioperative intraperitoneal chemotherapy, as well as intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC), are in the experimental phase [172, 173].

If tumour resection is not possible, a palliative surgical management is implemented, which can significantly affect the quality of life. It is used after exhausting all non-surgical methods, mainly if the tumour is responsible for mechanical jaundice, chronic pain and gastrointestinal obstruction or bleeding. The treatment method is individualised for each patient. If mechanical jaundice occurs, it is recommended that anastomosis between the bile duct and intestine, or draining of the bile tract, be performed. When an unresectable pancreatic tumour disturbs the passage of food through the duodenum, bypass surgery is recommended, usually gastrointestinal anastomosis. The method of surgical management of chronic pain is coeliac plexus neurolysis and/or thoracoscopic section of the splanchnic nerve.

Due to the limited number of studies conducted, no recommendations are available for patients with PNENs of unknown original site. In one of the studies the authors emphasise the significance of a surgical procedure in order to locate the primary tumour site, together with aggressive cytoreduction of the metastases, which could enable estimation of the survival and justification of the procedures [175] (*\*evidence level 3*).

Treatment of patients with PNETs should be comprehensive and conducted by a multidisciplinary team of doctors; the surgery should be performed in a centre specialising in pancreatic surgery (*\*evidence level 3*) [142].

#### **Minimal consensus statement on surgical treatment**

— *Accidentally detected, asymptomatic, non-functional neoplasms ≤ 2 cm in diameter, without evidence of histopathological and radiological malignancy may be observed, and the decision on the course of treatment should be taken by a multidisciplinary team of doctors experienced in the management of PNETs. Tumours > 2 cm require surgery, usually with lymphadenectomy.*

\*evidence level according to OCCEMB [252]



- In certain cases of small (< 2 cm) and well-demarcated PNETs, atypical resections may be performed, including enucleation and resection of the middle segment (it is necessary to collect the lymph nodes for histopathological examination). Circumferential resections and enucleations may be performed laparoscopically.
- Tumour resection should be considered even in the presence of metastases, including hepatic metastases, if they are potentially resectable and the patient meets the criteria for the surgery.
- It is believed that PNECs should not be operated on if disseminated metastases were found in the diagnostic process.
- In advanced functional PNETs resection is intended to reduce the symptoms and the tumour mass. Cytoreduction may be considered if removal of more than 90% of the tumour mass is possible, even if hepatic metastases are present (\*evidence level 3).
- In the case of unresectable hepatic metastases, the recommended palliative treatment includes HAE, TACE, or embolisation with the use of a radioisotope. RFA, cryoablation, and MWA can be applied in tumours  $\leq 5$  cm (\*evidence level 3).
- Liver transplantation is conducted in selected groups of patients with exacerbated symptoms associated with hormonal secretion. Patients who may benefit from transplantation are those under the age of 50 years, without metastases outside the liver, and with a low expression of Ki-67 (\*evidence level 3).

### 3.1.2. Surgical treatment of neuroendocrine neoplasms G3 NET and NECs

G3 NETs and NECs are very rare neoplasms, accounting for less than 1% of gastrointestinal malignant neoplasms. In up to 85% of cases, metastases are found at the moment of diagnosis (with distant metastases in 65% of cases) [37, 176]. Surgical treatment with the intent to treat is usually conducted in cases of locally advanced disease, where the chances of cure are limited [177]. According to present guidelines, in an advanced, metastatic disease, reduction of the tumour mass (cytoreductive surgery) and surgical resection of the metastases are not recommended [177]. The ablative therapy of metastases to liver are also not recommended [177].

According to other authors, aggressive locoregional therapy comprising surgery, RFA, and intrahepatic intra-arterial therapies is justified and safe in patients with GEP NETs of G3 and hepatic metastases: it improves the treatment outcomes [178, 179] (\*evidence level 3). The varied effectiveness of surgical treatment can be explained by the heterogeneous nature of G3 neuroendocrine neoplasms, which can be further classified on the basis of their biological characteristics.

### 3.2. Endoscopic treatment of PNENs

The treatment of PNENs is generally surgical, and endoscopic management is only symptomatic [6].

Endoscopy can be used for the symptomatic treatment of:

- mechanical jaundice (prosthesis of the biliary duct),
- obstruction of the gastrointestinal tract (prosthesis of the gastrointestinal tract lumen),
- control of gastrointestinal bleeding (the use of endoscopic haemostatic methods),
- pain (coeliac plexus neurolysis).

EUS-controlled coeliac plexus neurolysis (CPN), described for the first time in 1996, involving administration of 0.25% bupivacaine solution, followed by 98% alcohol, is an alternative method for the management of chronic pain associated with pancreatic tumours [6, 180].

It is also possible that in the future endoscopic EUS-controlled ablation of pancreatic NETs, involving the administration of cytotoxic agents or alcohol [181–184], or using thermoablation [185, 186], will become a minimally invasive therapeutic method for patients who cannot be treated surgically (evidence level 4).

### 3.3. Systemic therapy

Therapeutic management of patients with advanced non-resectable locoregional disease and/or distant metastases, or with generalised disease, should be determined by a multidisciplinary team of specialists, following the idea of the ENETS Centre of Excellence.

The choice of systemic therapy depends on the symptoms, staging of the disease, the level of radiotracer uptake in receptor scintigraphy, and histological characteristics of the tumour, as well as the patient's general condition and comorbidities [6].

Systemic treatment involves therapy with “cold” SST analogues (octreotide, lanreotide), molecularly targeted treatment (everolimus, sunitinib), and therapy with cytostatics, as well as a combination of the above.

#### 3.3.1. Somatostatin analogues

##### *Functional pancreatic neuroendocrine neoplasms (F-PNENs)*

Somatostatin analogues (octreotide, lanreotide) are first-line therapy in functional PNENs, regardless of the tumour size [7, 187] or tumour grading and stage of disease, to control the symptoms secondary to excessive hormone secretion, prior to a surgical therapy or in advanced stage. In case of a refractory syndrome, dose escalation above the maximum registered dose, or shortening the interval between the doses may be the option. Increasing the dose consists of reducing the intervals between injections of long-acting SSAs, from four to three weeks (to two weeks in clinical studies) [188, 189]. Use of pasireotide, a new SSA, can be considered in a treatment-resistant

\*evidence level according to OCCEMB [252]

carcinoid syndrome, if all other therapeutic options have failed, including ablation, TAE, and interferon alpha, and receiving the treatment as part of a clinical study is not possible.

Effect of SSAs in functional GEP NENs is discussed in “Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours)” (see p. 79–110), and below in *Pharmacotherapy in selected functional PNETs*.

#### **Non-functional pancreatic NENs (NF-PNENs)**

The first-line therapies in GEP NETs are SSAs, which have demonstrated antiproliferative effects in prospective phase III studies (CLARINET) [190–192].

Somatostatin analogues can be recommended in systemic treatments as a first-line therapy in pancreatic NETs with a low proliferation index ( $Ki-67 < 10\%$ ), due to their antiproliferative effect and limited toxicity, considered a class effect of SSAs. CLARINET provides direct evidence for the antiproliferative effect of lanreotide Autogel at a dose of 120 mg every four weeks, in PNETs, whereas there are no prospective, randomised studies on the use of octreotide LAR in pancreatic NETs. SSAs may be recommended to prevent the growth of the tumour, or inhibit it in the case of PNET. Simultaneously, based on the CLARINET study methodology, using lanreotide in the treatment of entero-pancreatic NETs of G1 and G2 is recommended up to a  $Ki-67$  of 10%, regardless of the level of hepatic tumor burden [193]. However, regarding all NENs, no experts have yet determined any particular limit value for recommendation of SSAs in antiproliferative therapy. An assessment in a prospective study is required to determine the proper  $Ki-67$  value to make the choice between SSAs and more aggressive therapeutic methods. Using lanreotide is recommended in patients with PNETs, regardless of the level of hepatic tumor burden, which is supported by the subgroup analysis in the CLARINET study [193]. Although the study did not demonstrate a benefit in overall survival because the subjects were allowed to cross-over from the placebo group to the open-label lanreotide group after progression, it is expected that lanreotide improves final outcomes of the treatment in patients with PNETs [194]. Therapy should start immediately after the diagnosis in cases of:

- a significant degree of hepatic tumor burden and extensive neoplastic lesions (they are the most important prognostic factors) [195];
- a primary tumour location in the pancreas (five-year overall survival in stage IV patients does not exceed 40–60%) [11, 196].

Despite a similar mechanism of action and comparable effectiveness of both SSAs (i.e. octreotide and lanreotide), the effect of octreotide on the control of the neoplastic process in PNETs has not been confirmed in a phase III study. However, it seems that, considering the conclusions from retrospective analyses indicating its effectiveness in this location, and indirect conclusions from the RADIANT-1 study, octreotide can be an acceptable therapeutic option in the antiproliferative treatment of PNETs [197, 198].

There is no data to support continued use of SSA therapy if the disease progresses during the treatment with the SSA (however, the therapy may be necessary to maintain the inhibitory effect on the secretion of bioactive substances/hormones in the case of functional tumours).

#### **Minimal consensus statement on the treatment with somatostatin analogues**

*Octreotide and lanreotide are effective in controlling clinical syndromes in functional NETs, and demonstrate an antiproliferative effect in well-differentiated NETs.*

*In PNETs, the antiproliferative action of the SSA is used both in the period of stabilisation, and progression of the disease. SSAs can be considered the first-line therapy for PNETs with a low proliferative index up to a  $Ki-67$  of 10%. Although the antiproliferative effectiveness of both available SSAs is considered a class effect, the scientific evidence supporting the use of lanreotide in the treatment of pancreatic NETs of G1 and G2, regardless of hepatic tumor burden, is more reliable.*

#### **Pharmacotherapy in selected functional PNETs**

##### **Insulinoma**

Pharmacological treatment of insulinoma is intended to prepare patients for a surgical procedure, or to achieve biochemical control in patients with an inoperable metastatic tumour. Apart from frequent meals of small volume, patients require intravenous glucose administration. Despite this treatment, hypoglycaemia often requires additional medications to control the serum glucose concentration. In most insulinoma patients, diazoxide proved to be effective in managing the symptoms of hypoglycaemia [11]. Diazoxide is used as a short-term treatment for patients with insulinoma awaiting surgery, or as a long-term treatment for patients with inoperable tumours. The recommended daily dose is 50–300 mg orally, maximally 600 mg/d. Usually this treatment is effective in controlling the symptoms of hypoglycaemia in patients with insulinoma. Adverse reactions, including oedema, increased body weight, hirsutism, and renal function disorders are common but usually tolerable.

Diazoxide therapy is often supported with hydrochlorothiazide at a dose of 25 mg/day, which prevents oedema and hyperkalaemia, and increases the hyperglycaemic effect of diazoxide.

\*evidence level according to OCEMB [252]

Verapamil and diphenylhydantoin (phenytoin) can be used to control glycaemia in some patients with insulinoma. Corticosteroids, including prednisolone, are also used in patients with insulinoma presenting refractory hypoglycaemia.

Somatostatin analogues (octreotide and lanreotide) are used in patients with confirmed expression of somatostatin receptors of type 2 on the tumour cells [199]. Approximately 30–50% of patients respond to SSAs, although this treatment may be ineffective in the control of hypoglycaemia, and the condition of some patients may deteriorate during the therapy [200–206]. In certain cases hypoglycaemia may increase due to inhibited glucagon secretion [9, 207].

In patients with malignant insulinomas, the medications used to control insulin secretion and hypoglycaemia include everolimus, mTOR inhibitor [9], effective in controlling hypoglycaemia in patients with malignant insulin-secreting tumours [200, 201, 203, 205, 208]. Sunitinib was also demonstrated to be effective in some patients.

#### **Gastrinoma**

Pharmacological treatment of gastrinoma is discussed in the section on gastroduodenal NENs (*see p.* 138–153).

**VIPoma** (symptoms: watery diarrhoea, hypokalaemia, achlorhydria [WDHA], Verner-Morrison syndrome): [6]

Hydration and supplementation of electrolytes are recommended because they may considerably improve the patient's clinical condition. In patients with VIPoma and with a rare life-threatening syndrome, administration of SSAs significantly alleviates the symptoms. In patients with life-threatening diarrhoea, resistant to maximum SSA doses, corticosteroids are used.

#### **Glucagonoma**

Somatostatin analogues are the first-line medications.

Zinc salts may be used in patients with glucagonoma to prevent further skin damage. Antithrombotic prophylaxis should be considered in all patients with NEN associated with an increased risk of thromboembolic complications (including glucagonoma).

Long-acting SSAs may be useful in patients with Cushing's syndrome and acromegaly associated with the ectopic secretion of ACTH, PTHrP, or GHRH [147].

### **3.3.2. Molecularly targeted treatment (targeted therapy)**

Currently, two **molecular targeted** drugs are available: m-TOR (mammalian target of rapamycin) pathway inhibitor, everolimus, and tyrosine multikinase inhibitor — sunitinib. The above drugs demonstrate a confirmed antiproliferative activity in the case of advanced (non-resectable or metastatic) progressive pancreatic NETs of G1/G2. The disease progression within the last

12 months should be assessed by radiological examination, according to the RECIST classification.

Based on the results of two placebo-controlled trials, a significantly prolonged median progression-free survival (PFS) by about 5.5–6 months was demonstrated for both therapies. Remission rates were 5% for everolimus and about 10% in the sunitinib group [210, 211].

Everolimus is an oral medication, recommended in a daily dose of 10 mg, which effectiveness was demonstrated in a clinical trials (RADIANT-1, RADIANT-3) involving patients with advanced, progressive G1/G2 pancreatic NETs. The beneficial effect of everolimus therapy on PFS consisted primarily of disease stabilisation or a small reduction in tumour mass and less frequent progression. In a subgroup analysis, the safety of everolimus in combination with octreotide was demonstrated. The correlation between PFS and previous or current SSA therapy, or previous chemotherapy, was not shown [198, 210, 212].

Everolimus demonstrated effectiveness in the treatment of insulinoma functional pancreatic tumours regarding control of glycaemia [213, 214], as well as in control of carcinoid syndrome symptoms (RADIANT-2) [215] and non-functional tumours (RADIANT-4) [216]. A similar hypoglycaemic effect was demonstrated in individual cases of PNETs treated with sunitinib [217]. Using targeted therapies in combination with SSAs in the treatment of functional NETs is a standard practice (inhibition of the tumour growth and improved control of the symptoms). Currently, clinical trials are being conducted comparing targeted treatment in combination with SSAs and monotherapy: targeted therapy vs. SSA (e.g. COOPERATE-2). The available data do not demonstrate benefits regarding PFS [218].

Using targeted therapies in combination with SSAs to obtain an antiproliferative effect in non-functional NETs requires further comparative studies.

Primary side effects associated with everolimus include mucositis, hyperglycaemia, and rare cases of non-infectious interstitial pneumonia.

Markedly increased toxicity was reported in patients previously treated either with PRRT and/or chemotherapy [219].

Sunitinib is an oral medication, used at a daily dose of 37.5 mg, which effectiveness in the treatment of PNETs was demonstrated in a placebo-controlled, multicentre, randomised, phase III study (PFS 11.4 vs. 5.5 months, HR 0.42; 95% CI 0.26–0.66,  $p < 0.001$ ) [211]. The side effects associated with sunitinib include fatigue syndrome, arterial hypertension, and congestive heart failure.

Targeted therapy is conducted until the disease progresses or unacceptable adverse events occur. Due to adverse reactions, dose reduction may be required

to 5 mg of everolimus per day or 25 mg of sunitinib per day [210, 211].

Due to a lack of direct comparative studies available (head-to-head) for these medications, the choice of targeted therapy is based on the medical history of the patient, comorbidities, the side effect profile, and availability of the treatment. The use of everolimus may be limited by comorbidities such as uncontrolled diabetes or lung diseases, and sunitinib therapy may be limited by serious cardiovascular complications.

Molecular targeted therapy may be used as first-line or second-line therapeutic options following chemotherapy or SSA therapy (cold or hot — PRRT). They should not be commonly used as first-line therapies, due to potential toxicity. There is no evidence allowing determination of a precise order for the various therapeutic options in the management of pancreatic NETs.

The best treatment sequence, considering survival, symptom control, and quality of life, is under discussion, but remains controversial [220].

We are awaiting the results of a cross-over study (SECTOR) assessing the antiproliferative effectiveness of everolimus compared against chemotherapy using the STZ/5-FU regimen in advanced pancreatic NETs [221].

At the moment, there is insufficient evidence supporting the use of other targeted therapies, such as bevacizumab, sorafenib, pazopanib, or axitinib, in the treatment of pancreatic NENs [222–224].

#### **Targeted treatment in NECs and NETs of G3.**

There is no evidence supporting the use of targeted therapies in NECs and NETs of G3 (clinical trials *in tractu* [www.clinical.trials.gov](http://www.clinical.trials.gov)).

#### **Minimal consensus statement on molecularly targeted treatments:**

- Everolimus and sunitinib are registered antiproliferative drugs used in advanced pancreatic NETs (\*evidence level 1), and constitute one of many therapeutic options, along with SSAs and systemic chemotherapy.
- Everolimus or sunitinib are recommended after a failure of SSA treatment, PRRT, or chemotherapy in pancreatic NETs of G1/G2. They can be considered as first-line therapies, especially if SSAs cannot be used, or in the case of intolerance, or contraindications for chemotherapy.
- Using targeted therapies in combination with SSAs in the treatment of functional NETs is a standard practice (inhibition of tumour growth and improved control of symptoms).
- There is no evidence supporting the effectiveness of targeted therapies in NECs and NETs of G3.

### **3.3.3. Chemotherapy**

Chemotherapy (ChTh) is one of many therapeutic options for neuroendocrine neoplasms of pancreatic

origin. Its place in the treatment algorithm depends on numerous factors, such as: histological characteristics of the neoplasm (differentiation, Ki-67%), significant tumor progression, the patient's general condition, and internal diseases, as well as the patient's preference.

#### **Adjuvant chemotherapy**

In pancreatic NETs of G1 and G2, there are no indications for adjuvant therapy following radical treatment.

In the case of pancreatic NETs of G3 (comprising well-differentiated or moderately differentiated neoplasms with Ki-67 > 20%, according to the new classification from 2017), there is no evidence for the use of adjuvant treatment. In certain cases, the adjuvant therapy can be considered individually.

Pancreatic NECs — considering the high recurrence rate after radical surgical treatment, in the case of aggressive neuroendocrine cancers, adjuvant chemotherapy with platinum and etoposide should be considered, although prospective clinical trials do not provide evidence for the benefits of such management, supported only by extrapolation of the treatment results in small-cell lung carcinomas [177].

#### **Palliative chemotherapy**

The results of clinical studies involving patients with pancreatic NETs of G1 and G2 reported objective response rates range between 43–70% achieved with palliative chemotherapy, [177, 225–228].

#### **G1 and G2 NETs**

Chemotherapy may be considered as the first-line treatment in NENs of pancreatic origin with Ki-67 expression of 5–20% in the case of:

- high tumor burden,
- presence of clinical symptoms of the disease,
- rapidly progressive disease (progression according to radiological assessment RECIST < 6–12 months),
- neoadjuvant treatment to increase the resectability of a locally advanced lesion [177].

#### **First-line treatment**

The regimens using streptozocin and 5-fluorouracil (STZ/5FU) or STZ and doxorubicin as an alternative regimen (STZ/DOX) are acknowledged therapeutic options, considered to be a gold standard. The use of doxorubicin is limited by a cumulative dose of 500 mg/m<sup>2</sup>, due to the risk of cardiotoxicity [225, 226]. Currently, streptozocin is not registered in Poland, and is not easily available.

\*evidence level according to OCEMB [252]



In such cases, an oral regimen with temozolomide and capecitabine (CAPTEM) can be used [177, 226].

It appears that a higher objective response rate following the use of temozolomide in pancreatic NENs may be correlated with expression of DNA-fixing enzyme — MGMT (O6-methylguanine DNA methyltransferase), which deficiency is more often observed in this location (approx. 50% of cases) [229–231]. However, determination of MGMT expression or methylation state is not currently recommended as a criterion for the use of chemotherapy.

### Second-line treatment

After the failure of a first-line therapy, there are alternative options of systemic treatment available for patients in good general condition:

- in the case of STZ-based chemotherapy, the use of temozolomide ± capecitabine (CAPTEM) should be considered [226];
- in the case of CAPTEM regimen (due to limited availability of STZ), chemotherapy with oxaliplatin + 5-FU or capecitabine (FOLFOX, XELOX) may be considered [232, 233].

### G3 NETs and NECs

Chemotherapy is the standard therapy of palliative treatment in advanced, poorly differentiated NECs.

#### a) Pancreatic NECs with Ki 67 > 55%

The standard management involves chemotherapy with PE (cisplatin + etoposide) or CE (carboplatin + etoposide) regimen. According to the results of the NORDIC NEC study, cisplatin might be replaced by carboplatin [234].

#### b) G3 NETs with Ki 67 < 55%

In the case of pancreatic G3 NETs (well-differentiated and moderately differentiated tumours with Ki-67 > 20%, distinguished as a separate group in the new AJCC 2017 classification) or gastro-entero-pancreatic NECs with Ki-67 < 55%, temozolomide + capecitabine (CAPTEM) or streptozocin with 5-fluorouracil (STZ + 5FU) chemotherapy should be preferably used [235, 236].

Second-line chemotherapy may be considered individually, exclusively in patients with good performance status [177].

Topotecan should not be used as it appears to be ineffective in therapy of NECs [235].

Regimens based on oxaliplatin (FOLFOX, XELOX), temozolomide (CAPTEM), or irinotecan (FOLFIRI, IP) are recommended [236–238].

In the case of a good response to the first-line chemotherapy, maintained for at least three months after completion of the treatment, and without therapy-related toxicity (e.g. neurotoxicity, ototoxicity, or renal

failure), reinduction according to the PE/CE regimen may be considered.

### Minimal consensus statement on chemotherapy

- *Advanced pancreatic NET of G1/2 — individualised treatment, depending on the proliferation fraction and disease symptoms; chemotherapy is not the standard first-line therapy (in patients with Ki67 < 10% treatment with SSAs [lanreotide, evidence level 2b] or targeted drugs — everolimus or sunitinib [\*evidence level 1b]). If the disease progresses rapidly threatens organ sufficiency, or symptoms occur, chemotherapy should be considered as the first-line treatment using a two-drug regimen, optimally based on streptozocin (\*evidence level 2b). Currently, the medication is unavailable in Poland; therefore, an alternative regimen based on temozolomide + capecitabine may be considered (CAPTEM).*
- *The basic treatment of pancreatic NECs involves cisplatin and etoposide-based chemotherapy (\*evidence level 3) as the first-line treatment, in particular with a high proliferation index Ki-67 > 55%. In the case of G3 NETs and NECs (Ki 67 < 55%) — STZ ± 5-Fu ± ADM chemotherapy may be considered, or alternatively, capecitabine and temozolomide (CAPTEM).*

### Minimal consensus statement on systemic therapies in pancreatic NENs:

*Functional NETs of G1/G2 — SSA (\*evidence level 1), and if the disease progresses, introduction of everolimus (\*evidence level 1).*

*Non-functional, advanced NET of G1/G2 — SSA (octreotide \*evidence level 2, lanreotide, \*evidence level 1) in the case of Ki67 < 10%, and if the disease threatens organ sufficiency, or is associated with pronounced symptoms, chemotherapy (optimally based on streptozocin combined with another medication, e.g. 5-FU, primarily in patients with G2 NET, or an alternative regimen: capecitabine and temozolomide) (\*evidence level 3), or targeted treatment (everolimus or sunitinib, primarily in G1 patients, \*evidence level 1).*

*The basic NEC treatment involves chemotherapy based on cisplatin and etoposide, and, in the case of progression or resistance to therapy, a regimen based on 5-fluorouracil and temozolomide derivatives (\*evidence level 3).*

### 3.4. Radioisotope treatment

Radioisotope therapy with labelled somatostatin analogues (PRRT, peptide receptor radionuclide therapy) is now one of the recognised forms of treatment, with an opportunity for the stabilisation or partial regression of the neoplastic disease, and less often for a complete remission [6, 239, 240]. The clinical data assessing the effectiveness of the therapy, including in PNETs, are cumulating with every passing year, which was reflected in the recently published ENETS guidelines, as well

\*evidence level according to OCEMB [252]

as in the European Association of Nuclear Medicine (EANM) guidelines [195, 241].

The recent ENETS guidelines regarding the use of various therapeutic forms as the first-line, second-line, and third-line therapies are based on studies published after 2012 (results of large, phase III clinical studies, i.e. PROMID, CLARINET, RADIANT-4, NETTER-1, TELESTRA, and SPINET). Unfortunately, there are no results of prospective studies using PRRT in pancreatic NETs available yet; in some published studies on the effectiveness of PRRT in this group of patients, the observed PFS is 29.7–39 months, and OS is 53–70 months [242–245].

PRRT is recommended in G1/G2 tumours after a failure of treatment with SSA, chemotherapy, or molecular targeted therapies. Earlier use of PRRT in a selected group of patients is considered to be justified, and similarly to GEP NETs in different locations, the therapy can be used without previous chemotherapy. In patients treated with chemotherapy before the radioisotope treatment, myelotoxicity and nephrotoxicity occur more often.

Based on the NETTER-1 study ( $^{177}\text{Lu}$ -DOTATATE vs. octreotide), ENETS recommends using PRRT as a second-line treatment in midgut neoplasms, after a failure of pharmacological treatment. PRRT in pancreatic NETs is considered to be a second- or third-line treatment.

The choice between different therapeutic options in pancreatic NETs, in particular regarding PRRT, also depends on their availability in a given country, and the decision and experience of the attending physician, as well as the choice/approval of the patient.

Similarly to other GEP NETs, the main indications for PRRT in the treatment of pancreatic NETs are advanced, inoperable G2 or G1 tumours. In individual cases, the treatment may be considered in PNETs of G3 with high expression of somatostatin receptors, especially in a progressing disease, when other therapeutic options have been exhausted [6, 8, 9]. Eligibility for PRRT treatment is in accordance with the principles described in the general section.

PRRT may also be considered as a neoadjuvant treatment in tumours inoperable due to a significant local advancement [6, 246]. Radiolabelled with  $^{90}\text{Y}$  and  $^{177}\text{Lu}$  somatostatin analogues were used in PNET as a neoadjuvant therapy. Among the patients who received PRRT as a neoadjuvant therapy for an inoperable primary tumour, there were individual cases of patients with hepatic metastases, who demonstrated not only tumour regression but also regression of the meta lesions after the radioisotope therapy [247]. Due to the small group of patients in whom this form of treatment was used there is no evidence supporting

introduction of PRRT before a non-surgical procedure to the management guidelines. However, this form of therapy may be considered individually, depending on the patient's clinical condition, disease stage, and the proliferation index of the neoplasm.

In the case of functional pancreatic NETs, radioisotope treatment is possible as a palliative therapy to reduce the symptoms of hormone secretion [6, 23, 135]. Based on individual reports in the literature, it is known that gastrinomas respond to therapy faster, but early progression is relatively frequent [6]. PRRT treatment may improve the control of hypoglycaemia in patients with malignant insulin-secreting tumours [74, 148, 248, 249].

PRRT may also be repeated during the subsequent progression of the disease, if stabilisation or remission was previously obtained with this method. It appeared that re-implementation of radioisotope treatment if somatostatin receptor expression is maintained by the tumour cells may prolong the patient's survival without significant exacerbation of the adverse reactions associated with this therapy [250].

Radioisotope therapy is increasingly often combined with "cold" SSAs (also in the case of non-functional tumours).

Among different forms of radioisotope treatment in NETs, including PNETs, radioembolisation of hepatic metastases with yttrium-labelled microspheres is used [142, 251]. Since there are no reports on the use of radioembolisation in a larger group of patients, further studies in this field are necessary.

### Place of radioisotope treatment in pancreatic NETs

Both in functional and non-functional PNETs, the basic form of treatment is surgery. In the case of functional pancreatic neoplasms, patients require additional therapy due to the presence of clinical symptoms.

In the case of advanced pancreatic NETs, treatment with long-acting SSAs is recommended as the first-line therapy. According to the CLARINET study results, they should be used primarily in tumours with Ki-67 of up to 10%. PRRT should be considered as the second-line treatment alternative to tyrosine kinase inhibitors/chemotherapy. PRRT as the first-line treatment can be used in malignant insulin-secreting tumours, following symptomatic therapy other than SSAs.

Chemotherapy may be introduced as the later-line treatment if the disease progresses, especially when SSTR expression is lost, or as the second-line treatment, depending on the centre's decision and experience of in the treatment of pancreatic G2 tumours.

The optimal treatment sequence may be established after the results of prospective studies are obtained.

\*evidence level according to OCEMB [252]

PRRT may be used in individual cases of pancreatic G3 NETs if a high expression of somatostatin receptors is confirmed and other forms of therapy are ineffective (\*evidence level 4).

**Minimal consensus statement on radioisotope therapies in pancreatic NENs**

Radioisotope therapy may be used in advanced, inoperable pancreatic NETs, especially G2 and G1, with the high somatostatin receptor expression confirmed in SRI examination (\*evidence level 3).

Qualification for PRRT: as in the general section of the guidelines.

PRRT is recommended after a failure of pharmacotherapy with SSAs.

PRRT may be considered as the second-line treatment, alternative to therapy with tyrosine kinase inhibitors.

## 4. Follow-up

The principles of treatment follow-up are the same as in GEP NENs, and have been discussed in detail in *Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours)*.

**Minimal consensus statement on follow-up:**

Monitoring of the treatment should be individualised according to histological differentiation of the NET (G1, G2, G3, or NEC) and the disease staging.

It comprises clinical examination, and determination of the concentration of CgA and specific markers (in functional tumours, depending on the clinical symptoms), as well as USG, CT/MRI, endoscopic, and functional (SRI) examinations. The frequency of examinations depends on the stage of the disease (three months for NECs and 6–12 months for G1, G2, or G3 NETs, or more frequently if disease progression is suspected).

The intervals in the follow-up may be extended if the disease is stabilised (especially in G1 NETs).

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